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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS	:	JONATHAN L. TILLY et al.
SERIAL NO.	:	09/503,852
FILING DATE	:	February 15, 2000
FOR	:	PROTECTION OF FEMALE REPRODUCTIVE SYSTEM FROM NATURAL AND ARTIFICIAL INSULTS
EXAMINER	:	L. DI NOLA-BARON
GROUP ART UNIT	:	1615

ASSISTANT COMMISSIONER FOR PATENTS
AND TRADEMARKS
Washington, D.C. 20231

APPEAL BRIEF

Real Party in Interest

The real parties in interest are:

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Sloan-Kettering Institute for Cancer Research and Massachusetts General Hospital are the co-assignees of the entire right, title, and interest in U.S. Patent Application Serial No. 09/503/852.

Related Appeal and Interferences

There are no related appeals or interferences.

Status of Claims

Claims 1-23, 27-36, and 46-71 are pending.
Claims 24-26 and 37-45 have been canceled.
Claims 1, 2, 4-18, 20-23, 27-36, and 46-71 are being appealed.
Claims 3 and 19 are not being appealed.

Status of Amendments

An Amendment under 35 U.S.C. §116 was filed but has not been entered. The last Amendment entered was filed on April 10, 2002 in response to the Office Action dated October 10, 2001. For the convenience of the Board of Appeals and Interferences, three copies of this Amendment and Office Action are enclosed.

Three copies of an Office Action, dated May 24, 2002, issued in response to the Amendment filed April 10, 2002 and containing a Final Rejection of all the pending claims, are also enclosed.

Three copies of the references Perez et al., Nat, Med. 3:1228-1232 (1997) ("Perez"): U.S. Patent No. 5,712,262 to Spiegel ("Spiegel"); and U.S. Patent No. 5,877,167 to Igarashi et al. ("Igarashi"), discussed herein, are also enclosed.

Summary of the Invention

The invention provides methods of protecting the female reproductive system against natural and artificial insults by administering a composition that contains an agent that antagonizes sphingomyelinase gene products.[1] Examples of artificial insults are chemical insults, radiation insults, and surgical insults.[2] Examples of natural insults are the consequences of aging, genetic background, physiological factors, and environmental factors.[3] A preferred agent is sphingosine-1-phosphate.[4] The female may be a woman.[5]

All of the appealed claims are directed to treatments that are administered either *in vivo* (*i.e.*, on or inside the body of a mammal) or *ex vivo* (*i.e.*, a composition is initially

[1] Specification, page 5, lines 3-5.
[2] Specification, page 5, lines 7-8.
[3] Specification, page 5, lines 8-10.
[4] Specification, page 6, lines 1-2.
[5] Specification, page 16, lines 18-20.

administered outside the body of the mammal, *e.g.*, to tissue or cells, but the treated tissue or cells are then returned to the body of the mammal). The present claims thus stand in sharp contrast to methods that are carried out *in vitro* (*i.e.*, completely outside the body of the mammal, in isolated tissues or cells which are not returned to the body of the mammal). Furthermore, the treatments of the present claims are given in response to an insult that occurs *in vivo*.

For claims 1, 2, 4-18, 20-23, and 62-72, the treatment is either *in vivo* or *ex vivo*. The treatment is given to protect a female reproductive system against an artificial insult that occurs *in vivo*.

For claims 27-36 and 46-61, the treatment is *in vivo*. Claims 27-32 recite that the composition is administered "to said mammal," and not, *e.g.*, to ovaries isolated from said mammal or to oocytes isolated from said mammal. Claims 33-36 recite that the composition is administered "to women." Claims 46-61 recite that the composition is administered "to a mammalian female patient." The treatments are given in response to an artificial or natural insult that occurs *in vivo*.

The present claims are directed to protecting the female reproductive system in various ways from artificial insults or natural insults where the insults occur *in vivo*.

The following illustrates how the elements of the appealed claims read on the specification.

Claim 1

Claim elements	Where found in the specification
Protecting a female reproductive system against an artificial insult	page 5, lines 3-4
Administering a composition comprising an agent that antagonizes one or more acid sphingomyelinase (*ASMase*) gene products	page 5, lines 4-5
in an amount sufficient to protect said female reproductive system from destruction caused by said artificial insult	page 5, lines 5-7
Wherein said administration is *in vivo* or *ex*	page 6, lines 2-3

vivo	

Claim 2

Claim elements	Where found in the specification
the artificial insult comprises chemical insult, radiation insult, surgical insult, or a combination thereof	page 5, lines 7-8

Claim 4

Claim elements	Where found in the specification
the chemical insult comprises cytotoxic factors, chemotherapeutic drugs, hormone deprivation, growth factor deprivation, cytokine deprivation, cell receptor antibodies, or a combination thereof	page 5, lines 12-13

Claim 5

Claim elements	Where found in the specification
the chemotherapeutic drug comprises; 5FU, vinblastine, actinomycin D, etoposide, cisplatin, methotrexate, doxorubicin, or a combination thereof	page 5, lines 14-15

Claim 6

Claim elements	Where found in the specification
the radiation insult comprises ionization radiation, x-ray, infrared radiation, ultrasound radiation, heat, or a combination thereof	page 5, lines 17-19

Claim 7

Claim elements	Where found in the specification
the radiation insult comprises an invasive radiation therapy, a non-invasive radiation therapy, or both	page 5, lines 18-19

Claim 8

Claim elements	Where found in the specification
the female reproductive system comprises ovaries	page 16, lines 15-17

Claim 9

Claim elements	Where found in the specification
the female reproductive system comprises oocytes	page 16, lines 15-17

Claim 10

Claim elements	Where found in the specification
the female is in a reproductive age	page 5, lines 20-21

Claim 11

Claim elements	Where found in the specification
the female is in a pre-reproductive age	page 5, lines 20-21

Claim 12

Claim elements	Where found in the specification
the female is in a post-reproductive age	page 5, lines 20-21

Claim 13

Claim elements	Where found in the specification
the agent comprises a small molecule compound	page 5, line 22

Claim 14

Claim elements	Where found in the specification
the small molecule compound comprises lysophospholipid	page 5, line 23

Claim 15

Claim elements	Where found in the specification
the lysophospholipid is a sphingolipid compound, or an analog thereof	page 5, line 23 to page 6, line 1

Claim 16

Claim elements	Where found in the specification
the sphingolipid compound is sphingosine-1-phosphate, or an analog thereof	page 6, lines 1-2

Claim 17

Claim elements	Where found in the specification
the composition is administered at least once from about fifteen days to about two days prior to exposure to said insult	page 17, lines 16-18

Claim 18

Claim elements	Where found in the specification
the composition is administered at about seven days to about two hours prior to exposure to said insult	page 17, lines 16-18

Claim 20

Claim elements	Where found in the specification
the composition is administered orally, intravascularly, intraperitoneally, subcutaneously, intramuscularly, intra-uterine, intra-ovarian, rectally, topically, or a combination thereof	page 6, lines 3-5

Claim 21

Claim elements	Where found in the specification
The artificial insult is a result of a therapy against a disease or a disorder	page 11, lines 11-12

Claim 22

Claim elements	Where found in the specification
The disease or disorder comprises, cancer, rheumatoid arthritis, angioplasy, or restenosis	page 11, lines 12-13

Claim 23

Claim elements	Where found in the specification
the cancer comprises; colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chondroma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma, acute lymphocytic leukemia and acute myelocytic leukemia, chronic leukemia and polycythemia vera, lymphoma (Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain diseases, or a combination thereof	page 11, line 13 to page 12, line 5

Claim 27

Claim elements	Where found in the specification
Preserving, enhancing, or reviving ovarian function in mammals	page 34, line 7
Administering a composition comprising sphingosine-1-phosphate, or an analog thereof to said mammal	page 6, lines 1-2
An amount effective to preserve, enhance, or revive ovarian function	page 5, lines 5-7

Claim 28

Claim elements	Where found in the specification
The mammal is in a reproductive age	page 5, lines 20-21

Claim 29

Claim elements	Where found in the specification
The mammal is in a pre-reproductive age	page 5, lines 20-21

Claim 30

Claim elements	Where found in the specification
The mammal is in a post-reproductive age	page 5, lines 20-21

Claim 31

Claim elements	Where found in the specification
The ovarian function comprises fertility, or normal menstrual cyclicity	page 20, lines 18-19

Claim 32

Claim elements	Where found in the specification
The mammal is a woman	page 16, lines 18-21

Claim 33

Claim elements	Where found in the specification
preventing or ameliorating menopausal syndromes in women	page 6, lines 13-14
administering to women, at predetermined intervals, a composition comprising sphingosine-1-phosphate, or an analog thereof	page 17, line 19 and page 6, lines 1-2
an amount effective to prevent or ameliorate at least one menopausal syndrome	page 6, lines 15-17

Claim 34

Claim elements	Where found in the specification
the women are pre-menopausal or post-menopausal women	page 16, lines 21-22

Claim 35

Claim elements	Where found in the specification
the menopausal syndromes comprise somatic disorders, cognitive disorders, emotional disorders, or a combination thereof	page 16, line 23 to page 17, line 3

Claim 36

Claim elements	Where found in the specification
the predetermined interval comprises daily, weekly, biweekly, or monthly intervals	page 17, line 10

Claim 46

Claim elements	Where found in the specification
protecting a female reproductive system from damage caused by treatment for a disease, disorder, or condition	page 11, lines 11-12
administering to a mammalian female patient in need thereof a treatment effective to treat a disease, disorder, or condition	page 16, lines 7-10
wherein said treatment is selected from the group consisting of chemical treatment, radiological treatment, surgical treatment, and combinations thereof	page 5, lines 7-8
administering to a mammalian female patient in need thereof a composition comprising an agent that antagonizes one or more acid sphingomyelinase (*ASMase*) gene products	page 5, lines 4-5
in an amount sufficient to protect the reproductive system of said female from damage caused by said chemical treatment, radiological treatment, surgical treatment, or a combination thereof	page 5, lines 5-7

Claim 47

Claim elements	Where found in the specification
the chemical treatment comprises administration of cytotoxic factors, chemotherapeutic drugs, hormone deprivation, growth factor deprivation, cytokine deprivation, cell receptor antibodies, or a combination thereof	page 5, lines 12-13

Claim 48

Claim elements	Where found in the specification
the chemotherapeutic drug comprises; 5FU, vinblastine, actinomycin D, etoposide, cisplatin, methotrexate, doxorubicin, or a combination thereof	page 5, lines 14-15

Claim 49

Claim elements	Where found in the specification
the radiation treatment comprises treatment with ionization radiation, x-ray, infrared radiation, ultrasound radiation, heat, or a combination thereof	page 5, lines 17-19

Claim 50

Claim elements	Where found in the specification
the agent comprises a small molecule compound	page 5, line 22

Claim 51

Claim elements	Where found in the specification
the small molecule compound comprises lysophospholipid	page 5, lines 23

Claim 52

Claim elements	Where found in the specification
the lysophospholipid is a sphingolipid compound, or an analog thereof	page 5, line 23 to page 6, line 1

Claim 53

Claim elements	Where found in the specification
the sphingolipid compound is sphingosine-1-phosphate, or an analog thereof	page 6, lines 20-21

Claim 54

Claim elements	Where found in the specification
the composition is administered prior to said treatment	page 17, lines 15-16

Claim 55

Claim elements	Where found in the specification
the composition is administered at least once from about fifteen days to about two days prior to said treatment	page 17, lines 14-18

Claim 56

Claim elements	Where found in the specification
the composition is administered at about seven days to about two hours prior to said insult treatment	page 17, lines 14-18

Claim 57

Claim elements	Where found in the specification
the composition is administered prior to and during said treatment	page 17, lines 18-20

Claim 58

Claim elements	Where found in the specification
the composition is administered during said treatment	page 5, lines 18-20

Claim 59

Claim elements	Where found in the specification
the composition is administered before, during, and/or after said treatment	page 17, lines 14-20

Claim 60

Claim elements	Where found in the specification
the composition is administered orally, intravascularly, intraperitoneally, subcutaneously, intramuscularly, intra-uterine, intra-ovarian, rectally, topically, or a combination thereof	page 6, lines 3-5

Claim 61

Claim elements	Where found in the specification
the disease, disorder, or condition comprises, cancer, rheumatoid arthritis, angioplasy, or restenosis	page 11, lines 12-13

Claim 62

Claim elements	Where found in the specification
protecting a female reproductive system against a natural insult	page 5, lines 3-4
administering a composition comprising an agent that antagonizes one or more acid sphingomyelinase (*ASMase*) gene products	page 5, lines 4-5
in an amount sufficient to protect said female reproductive system from pre-mature aging or destruction caused by said natural insult	page 5, lines 5-7
wherein said administration is *in vivo* or *ex vivo*	page 6, lines 2-3

Claim 63

Claim elements	Where found in the specification
the female reproductive system comprises ovaries and/or oocytes	page 16, lines 15-17

Claim 64

Claim elements	Where found in the specification
the female is in a reproductive age	page 5, lines 20-21

Claim 65

Claim elements	Where found in the specification
the female is in a pre-reproductive age	page 5, lines 20-21

Claim 66

Claim elements	Where found in the specification
the female is in a post-reproductive age	page 5, lines 20-21

Claim 67

Claim elements	Where found in the specification
the agent comprises a small molecule compound	page 5, line 22

Claim 68

Claim elements	Where found in the specification
The small molecule compound comprises lysophospholipid	page 5, line 23

Claim 69

Claim elements	Where found in the specification
The lysophospholipid is a sphingolipid compound, or an analog thereof	page 5, line 23 to line 6, page 1

Claim 70

Claim elements	Where found in the specification
The sphingolipid compound is sphingosine-1-phosphate, or an analog thereof	page 6, lines 1-2

Claim 71

Claim elements	Where found in the specification
The composition is administered orally, intravascularly, intraperitoneally, subcutaneously, intramuscularly, intra-uterine, intra-ovarian, rectally, topically, or a combination thereof	page 6, lines 3-5

Issues

The only issue is whether claims 1, 2, 4-18, 20-23, 27-36, and 46-71 are obvious under 35 U.S.C. §103(a) over Perez et al., Nat, Med. 3:1228-1232 (1997) ("Perez") in view of U.S. Patent No. 5,712,262 to Spiegel ("Spiegel") and further in view of U.S. Patent No. 5,877,167 to Igarashi et al. ("Igarashi").

Grouping of Claims

The claims stand or fall together.

Argument

Summary of the Examiner's position

The Examiner concluded that one of ordinary skill in the art would have combined Perez with Spiegel and Igarashi to arrive at the claimed invention. In the May 24, 2002 Office Action (containing the final rejection), the Examiner stated that:

- Perez provides a "strong impetus" to manipulate death effector pathways in oocytes as a potential means to overcome infertility associated with cancer treatment (page 5, lines 4-8).
- Spiegel teaches that sphingosine-1-phosphate retards apoptosis in degenerative diseases including aging (page 5, lines 8-9).
- Igarashi teaches that sphingosine-1-phosphate can be used to inhibit tumor cell chemoinvasion and provides dosages and routes of administration for the sphingosine-1-phosphate (page 5, lines 12-16).

After characterizing the cited references as summarized above, the Examiner went on to state that one of ordinary skill in the art would have combined Perez, Spiegel, and Igarashi to arrive at the claimed invention with a reasonable expectation of success, but did

not elaborate as to why the references would have been combined and why there would have been a reasonable expectation of success (page 5, line 17 to page 6, line 2).

Summary of the Appellants' position

The Appellants submit that the cited references do not make the claims obvious because:

- Perez is directed to the *in vitro* administration of sphingosine-1-phosphate to isolated oocytes to protect against an *in vitro* insult to those isolated oocytes.
- The claims are directed to *in vivo* or *ex vivo* (rather than *in vitro*) administration of agents such as sphingosine-1-phosphate to the female reproductive system (not to isolated oocytes) in order to protect against an insult to the female reproductive system (not to isolated oocytes).
- Perez contains explicit statements of doubt as to whether Perez's *in vitro* results with isolated oocytes can be successfully extrapolated to methods of treating the female reproductive system as opposed to isolated oocytes.
- Spiegel and Igarashi have absolutely nothing to do with oocytes or female reproductive systems and thus should not be combined with Perez. Even if so combined, Spiegel and Igarashi cannot overcome the statements of doubt in Perez as to treating female reproductive systems since Spiegel and Igarashi have nothing to do with female reproductive systems.

Detailed explanation of the Appellants' position

The cited references

Perez discloses studies in which sphingosine-1-phosphate was administered *in vitro* to isolated oocytes that were also exposed *in vitro* to doxorubicin. See page 1228, left column, second line from bottom, where Perez states that the oocytes that were studied were "harvested [*i.e.*, isolated] from superovulated adult female mice" and "maintained in human tubal fluid medium under standard *in vitro* conditions." See page 1229, Figure 2, and the discussion of Figure 2 in the left column, where Perez states that sphingosine-1-phosphate was administered to the isolated oocytes. Perez did not disclose studies in which sphingosine-1-phosphate was administered either *in vivo* or *ex vivo*. In Perez, the oocytes were never returned to the body, but were merely observed *in vitro*. Moreover, the insult

(doxorubicin exposure) to the oocytes that were administered sphingosine1-phosphate occurred *in vitro*.

Spiegel is directed to "methods of retarding apoptosis in degenerative diseases, including neurodegenerative diseases and aging, ..." (May 24, 2002 Office Action, page 3, 2nd paragraph). Speigel disclosed the use of sphingosine-1-phosphate.

Igarashi is directed to "a method of inhibiting tumor cell chemoinvasion." (May 24, 2002 Office Action, page 3, 3rd paragraph). Igarashi disclosed the use of sphingosine-1-phosphate.

Spiegel and Igarashi do not discuss oocytes or female reproductive systems.

Differences between the claims and the cited references

The present claims are directed to "methods of protecting [a] female reproductive system, preserving or reviving ovarian function, or ameliorating menopausal syndromes in women" (may 24, 2002 Office Action, page 2, lines 19-20). Since these methods do not encompass treating isolated oocytes *in vitro*, all of these methods require the *in vivo* or *ex vivo* use of compositions (including sphingosine-1-phosphate) to treat the female reproductive system (as opposed to isolated cells from that system). Moreover, the present claims are directed to treatments that are given in response to insults that occur *in vivo* rather than *in vitro*.

Perez is directed only to the *in vitro* use of sphingsine-1-phosphate (i.e., administered to isolated oocytes) and not its *in vivo* or *ex vivo* use. The use of sphigosine-1-phosphate in Perez is limited to use in conjunction with *in vitro* insults. Spiegel and Igarashi are not directed to treating the female reproductive system in any manner.

The rejection for obviousness

The Examiner concluded that one of ordinary skill in the art would have combined Perez with Spiegel and Igarashi to arrive at the claimed invention. The reasons for this conclusion are given in the May 24, 2002 Office Action at page 5, line 4 to page 6, line 2:

> Perez et al teaches that exposure of women to a wide spectrum of agents that damage the ovary generally leads to irreversible serility (See e.g., p. 1228) and the data from the study provide a strong impetus to manipulate death effector pathways in oocytes, in vivo, as a potential means to overcome infertility associated with cancer treatment (See e.g., p. 1231). Spiegel teaches the use of sphingosine-1-phosphate (SPP) to retard apoptosis in degeneratice diseases, including aging, which is defined by Applicant as a natural insult (See Applicant's specification, p. 15). Additionally, Spiegel teaches that SPP may be administered to the epithelial tissues, such as the rectum and the vagina (See e.g., Col. 1, line 46 to col. 2, line 26). Igarashi et al. provides methods of inhibiting tumor cell chemoinvasion, comprising administering to a host in need of treatment an inhibitory amount of sphingosine-1-phosphate and teaches that said inhibitory amount can be determined using art-recognized methods, such as dose response curves, or clinical trials, and sphingosine-1-phosphate can be administered orally, parenterally and topically (See e.g., col.7, lines 32-65). Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to combine the teachings of Perez et al. and Spiegel to device [sic, devise?] methods of protecting the female reproductive system, reviving the ovarian function or ameliorating menopausal syndromes in women, comprising administering SPP compositions, and determining the mode and dosage of adminstration according to the teachings of Igarashi et al. The expected result would have been a successful method of protecting a female reproductive system against natural or artificial insults.

Why the rejection should be withdrawn

The cited references do not provide a reasonable expectation of success for the claimed invention

The Applicants contend that Perez, Spiegel, and Igarashi, in any combination, do not provide a reasonable expectation of success for the claimed invention.

It is well settled that a finding of obvious requires that the cited references provide a reasonable expectation of success for the claimed invention. It is not sufficient that the references make it obvious to try to make the claimed invention. See, *e.g.*, In re Vaeck, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991), where the Federal Circuit said:

> [A] proper analysis under §103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of

> ordinary skill would have a reasonable expectation of success. *See In re Dow Chemical Co.,* 837 F2d 469, 473, 5 U.S.P.Q. 2d 1529, 1531 (Fed. Cir. 1988). [emphasis added]

Perez alone cannot provide a reasonable expectation of success for the claimed invention because:

- Perez is directed to an *in vitro* method (administering sphingosine-1-phosphate to isolated oocytes) to protect against an *in vitro* insult (administering doxorubicin to isolated oocytes).
- The present claims do not encompass *in vitro* methods to protect against *in vitro* insults.
- Perez contains explicit statements of doubt as to whether Perez's *in vitro* results with isolated oocytes can be extrapolated to *in vivo* treatment of the female reproductive system as in the present claims. For example, Perez made it clear that *in vitro* effects are not predictive of *in vivo* successes such as preserving ovarian function. See page 1231, sentence bridging left and right columns:

> Despite the significant advances made by this study in defining the biochemical and genetic pathways involved in oocyte destruction following eposure to anticancer drugs, future long-term studies are required to confirm that inhibiting germ cell apoptosis will preserve ovarian function. [emphasis added]

Perez also taught that *in vivo* treatments of the female reproductive system (*e.g.*, preserving its fertility) require an effect not just on oocytes, but also on the follicles that support oocytes. See page 1230, lines 6-7: "[F]ertility preservation would require maintenance of the entire follicle and not solely the oocyte." Perez, page 1230, col. 1, lines 6-7. Perez contains no demonstration of the effects of sphingosine-1-phosphate on follicles and thus cannot provide a reasonable expectation of success for treatments that depend on effects on follicles.

With respect to what implications Perez's *in vitro* results have for *in vivo* methods such as those presently claimed, the Examiner stated: "[T]he data from the study [*i.e.*, from Perez] provide a strong impetus to manipulate death effector pathways in oocytes, in vivo, as a potential means to overcome infertility associated with cancer treatment." [first underlining added] (May 24, 2002 Office Action, page 3, lines 5-7 and page 5, lines 6-8)

The Applicants believe that the statement quoted above demonstrates at most that Perez makes it obvious to try the claimed invention. This is supported by the Examiner's use

of the word "impetus" which speaks to motivation or suggestion rather than expectation of success.

The Examiner did not argue that Perez alone provided a reasonable expectation of success. The Examiner instead argued that it was the combination of Spiegel and Igarashi with Perez that provided a reasonable expectation of success. There is only one statement in the Office Action dated May 24, 2002 that contains a reasoned argument as to why the Spiegel and Igarashi references might provide a reasonable expectation of success for the claimed invention. See page 4, 2nd paragraph, lines 5-9:

> Because of the teachings of Spiegel, that sphingosine-1-phosphate is effective in treating aging diseases, and the teachings of Igarashi et al., that sphingosine-1-phosphate inhibits tumor cell chemoinvasion, one of ordinary skill in the art would have a reasonable expectation that the methods claimed in the instant application would be successful.

In other words, the Examiner is relying on references directed to neurodegenerative aging diseases and the metastasis of tumor cells in order to provide a reasonable expectation of success for an invention directed to the *in vivo* protection of the female reproductive tract! These three types of health problems have no obvious connection and the Examiner has not provided an explanation of why they might be connected. The Applicants do not understand how the expressions of doubt as to reasonable expectation of success in Perez quoted above can be negated by two references that are directed to entirely different health problems from those of both Perez and the present claims.

The cited references should not be combined

That the Examiner could not explain how the cited references might provide a reasonable expectation of success is not surprising when one considers the content of the references. Spiegel and Igarashi cannot bridge the gap between Perez's *in vitro* results in oocytes and the Applicants' *in vivo* invention directed to female reproduction because Spiegel and Igarashi have absolutely nothing to do with oocytes or female reproduction.

Spiegel is directed to "methods of retarding apoptosis in degenerative diseases, including neurodegenerative diseases and aging, ..." (May 24, 2002 Office Action, page 3, 2nd paragraph). Igarashi is directed to "a method of inhibiting tumor cell chemoinvasion." (May

24, 2002 Office Action, page 3, 3rd paragraph). The Examiner never contends that Spiegel or Igarashi discuss oocytes or female reproduction.

Spiegel and Igarashi are not directed to the field of the Applicants' invention, mammalian female reproduction. Nor are Spiegel and Igarashi directed to the particular problems solved by the present claims: protecting a female reproductive system against an artificial insult (claims 1, 2, 4-18, and 20-23); preserving, enhancing, or reviving ovarian function (claims 27-32); preventing or ameliorating menopausal syndromes (claims 32-36); protecting a female reproductive system from damage caused by treatment for a disease, disorder, or condition (claims 46-61); and protecting a female reproductive system against an natural insult (claims 62-72).

References that are directed neither to the field of the applicant's invention or to the particular problem with which the applicant is concerned may not be used to support an obviousness rejection. See, *e.g.*, In re Oetiker, 977 F.2d 1443, 1447, 24 USPQ2d 1443:

> In order to rely on a reference as a basis for rejection of the applicant's invention, the reference must either be in the field of the applicant's endeavor, or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned.

Since Spiegel and Igarashi are directed neither to the field of the Applicants' invention or to the particular problem with which the Applicants were concerned, Spiegel and Igaraashi should not have been combined with Perez.

In view of the above, the Appellants submit that it has been demonstrated that claims 1, 2, 4-18, 20-23, 27-36, and 46-71 are not obvious under 35 U.S.C. §103(a) over Perez, Spiegel, and Igarashi.

CONCLUSION

For the reasons discussed above, the Appellants respectfully request that the Board of Patent Appeals and Interferences reverse the rejection of claims 1, 2, 4-18, 20-23, 27-36, and 46-71 under 35 U.S.C. §103(a).

Respectfully submitted,

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APPENDIX

1. A method of protecting a female reproductive system against an artificial insult comprising: administering a composition comprising an agent that antagonizes one or more acid sphingomyelinase (*ASMase*) gene products, in an amount sufficient to protect said female reproductive system from destruction caused by said artificial insult, wherein said administration is *in vivo* or *ex vivo*.

2. The method of claim 1, wherein said artificial insult comprises chemical insult, radiation insult, surgical insult, or a combination thereof.

4. The method of claim 2, wherein said chemical insult comprises cytotoxic factors, chemotherapeutic drugs, hormone deprivation, growth factor deprivation, cytokine deprivation, cell receptor antibodies, or a combination thereof.

5. The method of claim 4, wherein said chemotherapeutic drug comprises; 5FU, vinblastine, actinomycin D, etoposide, cisplatin, methotrexate, doxorubicin, or a combination thereof.

6. The method of claim 2, wherein said radiation insult comprises ionization radiation, x-ray, infrared radiation, ultrasound radiation, heat, or a combination thereof.

7. The method of claim 2, wherein said radiation insult comprises an invasive radiation therapy, a non-invasive radiation therapy, or both.

8. The method of claim 1, wherein said female reproductive system comprises ovaries.

9. The method of claim 1, wherein said female reproductive system comprises oocytes.

10. The method of claim 1, wherein said female is in a reproductive age.

11. The method of claim 1, wherein said female is in a pre-reproductive age.

12. The method of claim 1, wherein said female is in a post-reproductive age.

13. The method of claim 1, wherein said agent comprises a small molecule compound.

14. The method of claim 13, wherein said small molecule compound comprises lysophospholipid.

15. The method of claim 14, wherein said lysophospholipid is a sphingolipid compound, or an analog thereof.

16. The method of claim 15, wherein said sphingolipid compound is sphingosine-1-phosphate, or an analog thereof.

17. The method of claim 1, wherein said composition is administered at least once from about fifteen days to about two days prior to exposure to said insult.

18. The method of claim 17, wherein said composition is administered at about seven days to about two hours prior to exposure to said insult.

20. The method of claim 1, wherein said composition is administered orally, intravascularly, intraperitoneally, subcutaneously, intramuscularly, intra-uterine, intra-ovarian, rectally, topically, or a combination thereof.

21. The method of claim 1, wherein said artificial insult is a result of a therapy against a disease or a disorder.

22. The method of claim 21, wherein said disease or disorder comprises, cancer, rheumatoid arthritis, angioplasy, or restenosis.

23. The method of claim 22, wherein said cancer comprises; colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chondroma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary

carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma, acute lymphocytic leukemia and acute myelocytic leukemia, chronic leukemia and polycythemia vera, lymphoma (Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain diseases, or a combination thereof.

27. A method of preserving, enhancing, or reviving ovarian function in mammals comprising: administering a composition comprising sphingosine-1-phosphate, or an analog thereof to said mammal in an amount effective to preserve, enhance, or revive ovarian function.

28. The method of claim 27, wherein said mammal is in a reproductive age.

29. The method of claim 27, wherein said mammal is in a pre-reproductive age.

30. The method of claim 27, wherein said mammal is in a post-reproductive age.

31. The method of claim 27, wherein said ovarian function comprises fertility, or normal menstrual cyclicity.

32. The method of claim 27, wherein said mammal is a woman.

33. A method of preventing or ameliorating menopausal syndromes in women, comprising administering to women, at predetermined intervals, a composition comprising sphingosine-1-phosphate, or an analog thereof in an amount effective to prevent or ameliorate at least one menopausal syndrome.

34. The method of claim 33, wherein said women are pre-menopausal or post-menopausal women.

35. The method of claim 33, wherein said menopausal syndromes comprise somatic disorders, cognitive disorders, emotional disorders, or a combination thereof.

36. The method of claim 33, wherein said predetermined interval comprises daily, weekly, biweekly, or monthly intervals.

46. A method for protecting a female reproductive system from damage caused by treatment for a disease, disorder, or condition, comprising administering to a mammalian female patient in need thereof (a) a treatment effective to treat a disease, disorder, or condition, wherein said treatment is selected from the group consisting of chemical treatment, radiological treatment, surgical treatment, and combinations thereof and (b) a composition comprising an agent that antagonizes one or more acid sphingomyelinase (*ASMase*) gene products, in an amount sufficient to protect the reproductive system of said female from damage caused by said chemical treatment, radiological treatment, surgical treatment, or a combination thereof .

47. The method of claim 46, wherein said chemical treatment comprises administration of cytotoxic factors, chemotherapeutic drugs, hormone deprivation, growth factor deprivation, cytokine deprivation, cell receptor antibodies, or a combination thereof.

48. The method of claim 47, wherein said chemotherapeutic drug comprises; 5FU, vinblastine, actinomycin D, etoposide, cisplatin, methotrexate, doxorubicin, or a combination thereof.

49. The method of claim 46, wherein said radiation treatment comprises treatment with ionization radiation, x-ray, infrared radiation, ultrasound radiation, heat, or a combination thereof.

50. The method of claim 46, wherein said agent comprises a small molecule compound.

51. The method of claim 50, wherein said small molecule compound comprises lysophospholipid.

52. The method of claim 51, wherein said lysophospholipid is a sphingolipid compound, or an analog thereof.

53. The method of claim 52, wherein said sphingolipid compound is sphingosine-1-phosphate, or an analog thereof.

54. The method of claim 46, further wherein said composition is administered prior to said treatment.

55. The method of claim 54, wherein said composition is administered at least once from about fifteen days to about two days prior to said treatment.

56. The method of claim 54, wherein said composition is administered at about seven days to about two hours prior to said insult treatment.

57. The method of claim 46, further wherein said composition is administered prior to and during said treatment.

58. The method of claim 46, further wherein said composition is administered during said treatment.

59. The method of claim 46, wherein said composition is administered before, during, and/or after said treatment.

60. The method of claim 46, wherein said composition is administered orally, intravascularly, intraperitoneally, subcutaneously, intramuscularly, intra-uterine, intra-ovarian, rectally, topically, or a combination thereof.

61. The method of claim 46, wherein said a disease, disorder, or condition comprises, cancer, rheumatoid arthritis, angioplasy, or restenosis.

62. A method of protecting a female reproductive system against a natural insult comprising: administering a composition comprising an agent that antagonizes one or more acid sphingomyelinase (*ASMase*) gene products, in an amount sufficient to protect said female reproductive system from pre-mature aging or destruction caused by said natural insult, wherein said administration is *in vivo* or *ex vivo*.

63. The method of claim 62, wherein said female reproductive system comprises ovaries and/or oocytes.

64. The method of claim 62, wherein said female is in a reproductive age.

65. The method of claim 62, wherein said female is in a pre-reproductive age.

66. The method of claim 62, wherein said female is in a post-reproductive age.

67. The method of claim 62, wherein said agent comprises a small molecule compound.

68. The method of claim 62, wherein said small molecule compound comprises lysophospholipid.

69. The method of claim 62, wherein said lysophospholipid is a sphingolipid compound, or an analog thereof.

70. The method of claim 62, wherein said sphingolipid compound is sphingosine-1-phosphate, or an analog thereof.

71. The method of claim 62, wherein said composition is administered orally, intravascularly, intraperitoneally, subcutaneously, intramuscularly, intra-uterine, intra-ovarian, rectally, topically, or a combination thereof.

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/501,652	02/15/00	TILLY	1 [illegible]/20

02352?
KENYON & KENYON
1500 K STREET, N.W., SUITE [illegible]
WASHINGTON DC 20005

HM12/1019

EXAMINER	
NOLA BARON, L	
ART UNIT	PAPER NUMBER
1615	9

DATE MAILED: 10/19/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/503,852	Tilly et al.	
	Examiner	Art Unit	
	Liliana Di Nola-Baron	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *37-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, claims 1-36, in Paper No. 8 is acknowledged. Accordingly, claims 37-45 are withdrawn from consideration.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Perez et al. in view of Spiegel and further in view of Igarashi et al.

The claimed invention refers to methods of protecting female reproductive system, preserving or reviving ovarian function, or ameliorating menopausal syndromes in women, comprising administering a composition comprising sphingosine-1-phosphate (SPP).

Perez et al. indicates that conventional cancer therapies kill normal cells and one of the most sensitive noncancerous cell type is the ovarian germ cell, and teaches that apoptosis induced by doxorubicin is blocked by sphingosine-1-phosphate (See e.g., p. 1228 and Abstract).
Perez et al. does not specify the method and dosage of administration of compositions comprising SPP.

Spiegel provides methods of retarding apoptosis in degenerative diseases, including neurodegenerative diseases and aging, by administration of sphingosine-1-phosphate and derivatives thereof (See e.g., col. 1, lines 9-17). Spiegel teaches that compositions containing SPP may be administered directly to the cells or parenterally to obtain concentrations of 0.1-100 μM (See e.g., col. 1, line 46 to col. 2, line 42).

Igarashi et al. discloses a method of inhibiting tumor cell chemoinvasion, comprising contacting the tumor cells with an inhibitory amount of sphingosine-1-phosphate (See e.g., col. 1, line 57 to col. 2, line 48). Igarashi et al. teaches that suitable doses of sphingosine-1-phosphate depend upon the particular medical application and that the number of doses, daily dosage and course of treatment may vary from individual to individual (See e.g., col. 7, lines 57-63).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to apply the teachings of Perez et al. and Spiegel to device methods of protecting the female reproductive system, reviving the ovarian function or ameliorating menopausal syndromes in women, comprising administering SPP compositions, and determining the mode and dosage of administration according to the teachings of Igarashi et al. Because of the teachings of Spiegel, that sphingosine-1-phosphate is effective in treating neurodegenerative and aging diseases, and the teachings of Igarashi et al., that sphingosine-1-phosphate inhibits tumor cell chemoinvasion, one of ordinary skill in the art would have a reasonable expectation that the methods claimed in the instant application would be successful. Therefore the invention

as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Liliana Di Nola-Baron whose telephone number is 703-308-8318. The examiner can normally be reached on Monday through Thursday, 5:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on 703-308-2927. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3592 for regular communications and 703-305-3592 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 308-1234/ 1235.

October 4, 2001

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS	:	JONATHAN L. TILLY et al.
SERIAL NO.	:	09/503,852
FILING DATE	:	February 15, 2000
FOR	:	PROTECTION OF FEMALE REPRODUCTIVE SYSTEM FROM NATURAL AND ARTIFICIAL INSULTS
EXAMINER	:	L. DI NOLA-BARON
GROUP ART UNIT	:	1615

ASSISTANT COMMISSIONER FOR PATENTS
AND TRADEMARKS
Washington, D.C. 20231

AMENDMENT AND RESPONSE UNDER 37 C.F.R. § 1.111 and PETITION FOR EXTENSION OF TIME

SIR:

In response to the Office Action dated 10 October 2001, and in accordance with 37 C.F.R. § 1.111, Applicants respectfully request entry of the present Amendment and reconsideration of the above-identified application.

Pursuant to 37 C.F.R. § 1.136(a), Applicants hereby respectfully request a three-month extension of time for responding to this Office Action, thus extending the period for response up to and including 10 April 2002. The Commissioner is hereby authorized to charge the appropriate small entity fee for this three-month extension, and to charge any other fees which may be due in connection with the filing of this response, or to credit any overpayment, to Kenyon & Kenyon's Deposit Account No. 11-0600.

AMENDMENT

Please amend the above-identified application as follows:

IN THE CLAIMS:

Please cancel Claims 24-26 and 37-45, without prejudice or disclaimer.

Please amend Claims 1, 3, 27, and 33 as follows:

1. (Amended) A method of protecting a female reproductive system against an artificial insult comprising: administering a composition comprising an agent that antagonizes one or more acid sphingomyelinase (*ASMase*) gene products, in an amount sufficient to protect said female reproductive system from destruction caused by said artificial insult, wherein said administration is *in vivo* or *ex vivo*.

3. (Amended) The method of claim 62 wherein said natural insult is a consequence of aging, genetic background, physiological factors, environmental factors, or a combination thereof.

27. (Amended) A method of preserving, enhancing, or reviving ovarian function in mammals comprising: administering a composition comprising sphingosine-1-phosphate, or an analog thereof to said mammal in an amount effective to preserve, enhance, or revive ovarian function.

33. (Amended) A method of preventing or ameliorating menopausal syndromes in women, comprising administering to women, at predetermined intervals, a composition comprising sphingosine-1-phosphate, or an analog thereof in an amount effective to prevent or ameliorate at least one menopausal syndrome.

Please add new Claims 46-71, as follows:

--46. (New) A method for protecting a female reproductive system from damage caused by treatment for a disease, disorder, or condition, comprising administering to a mammalian female patient in need thereof (a) a treatment effective to treat a disease, disorder,

or condition, wherein said treatment is selected from the group consisting of chemical treatment, radiological treatment, surgical treatment, and combinations thereof and (b) a composition comprising an agent that antagonizes one or more acid sphingomyelinase (*ASMase*) gene products, in an amount sufficient to protect the reproductive system of said female from destruction caused by said chemical treatment, radiological treatment, surgical treatment, or a combination thereof.

47. (New) The method of claim 46, wherein said chemical treatment comprises administration of cytotoxic factors, chemotherapeutic drugs, hormone deprivation, growth factor deprivation, cytokine deprivation, cell receptor antibodies, or a combination thereof.

48. (New) The method of claim 47, wherein said chemotherapeutic drug comprises; 5FU, vinblastine, actinomycin D, etoposide, cisplatin, methotrexate, doxorubicin, or a combination thereof.

49. (New) The method of claim 46, wherein said radiation treatment comprises treatment with ionization radiation, x-ray, infrared radiation, ultrasound radiation, heat, or a combination thereof.

50. (New) The method of claim 46, wherein said agent comprises a small molecule compound.

51. (New) The method of claim 50, wherein said small molecule compound comprises lysophospholipid.

52. (New) The method of claim 51, wherein said lysophospholipid is a sphingolipid compound, or an analog thereof.

53. (New) The method of claim 52, wherein said sphingolipid compound is sphingosine-1-phosphate, or an analog thereof.

54. (New) The method of claim 46, further wherein said composition is administered prior to said treatment.

55. (New) The method of claim 54, wherein said composition is administered at least once from about fifteen days to about two days prior to said treatment.

56. (New) The method of claim 54, wherein said composition is administered at about seven days to about two hours prior to said insult treatment.

57. (New) The method of claim 46, further wherein said composition is administered prior to and during said treatment.

58. (New) The method of claim 46, further wherein said composition is administered during said treatment.

59. (New) The method of claim 46, wherein said composition is administered before, during, and/or after said treatment.

60. (New) The method of claim 46, wherein said composition is administered orally, intravascularly, intraperitoneally, subcutaneously, intramuscularly, intra-uterine, intra-ovarian, rectally, topically, or a combination thereof.

61. (New) The method of claim 46, wherein said a disease, disorder, or condition comprises, cancer, rheumatoid arthritis, angioplasy, or restenosis.

62. (New) A method of protecting a female reproductive system against a natural insult comprising: administering a composition comprising an agent that antagonizes one or more acid sphingomyelinase (*ASMase*) gene products, in an amount sufficient to protect said female reproductive system from pre-mature aging or destruction caused by said natural insult, wherein said administration is *in vivo* or *ex vivo*.

63. (New) The method of claim 62, wherein said female reproductive system comprises ovaries and/or oocytes.

64. (New) The method of claim 62, wherein said female is in a reproductive age.

65. (New) The method of claim 62, wherein said female is in a pre-reproductive age.

66. (New) The method of claim 62, wherein said female is in a post-reproductive age.

67. (New) The method of claim 62, wherein said agent comprises a small molecule compound.

68. (New) The method of claim 62, wherein said small molecule compound comprises lysophospholipid.

69. (New) The method of claim 62, wherein said lysophospholipid is a sphingolipid compound, or an analog thereof.

70. (New) The method of claim 62, wherein said sphingolipid compound is sphingosine-1-phosphate, or an analog thereof.

71. (New) The method of claim 62, wherein said composition is administered orally, intravascularly, intraperitoneally, subcutaneously, intramuscularly, intra-uterine, intra-ovarian, rectally, topically, or a combination thereof.--

REMARKS

Claims 24-26 and 37-45 have been canceled without prejudice or disclaimer. Claims 37-45 have been canceled as they are withdrawn from consideration as the result of a restriction requirement. The limitations of claims 25 and 26 have been incorporated into Claim 1.

Claims 1 and 3 have been amended and new claims 62-71 have been added to divide natural and artificial insults into two claim groups for ease of prosecution; the scope of the claims as a whole has not been changed by these amendments.

Claims 27 and 33 have been amended to more particularly point out and distinctly claim embodiments of the invention. The scope of these claims has not been changed by these amendments.

New claims 46-61 have been added to more particularly point out and distinctly claim embodiments of the invention related to the embodiments of the claims remaining after the restriction requirement.

These amendments, cancellations, and additions are fully supported by the application as-filed, and no new matter is added. Claims 1- 23, 27-36, and 46-71 are currently pending.

Claims 1-36 stand rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over "Apoptosis-associated signaling pathways are required for chemotherapy-mediated female germ cell destruction" authored by Perez *et al.* ("Perez") in view of U.S. Patent No. 5,712,262 to Spiegel ("Spiegel") and further in view of U.S. Patent No. 5,877,167 to Igarashi *et al.* ("Igarashi"). This ground of rejection, insofar as the Examiner may consider it applicable to any claim in this application upon entry of the present amendment, is respectfully traversed and reconsideration thereof is respectfully requested. Applicants also assert that new claims 46-71 are patentable over the references, alone or in any combination, for at least the same reasons that Claims 1- 23 and 27-36 are patentable over any of the references alone or in any combination.

Rejection of Claims 1-36 Under 35 U.S.C. §103(a)

Claims 1-36 were rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over Perez in view of Spiegel and further in view of Igarashi. The Office Action concludes that the present invention allegedly would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made. Applicants respectfully submit that a *prima*

facie case of obviousness has not been established for at least the following reasons.

The pending claims are directed to methods of protecting a female reproductive system from natural insults or from artificial insults, such as damage caused by treatment for a disease, disorder, or condition; preserving, enhancing, or reviving ovarian function in mammals; and preventing or ameliorating menopausal syndromes in women comprising administration of an agent that antagonizes one or more acid sphingomyelinase (*ASMase*) gene products. Each of the claims requires that the agent be administered in one of the following amounts: an amount effective to protect the female reproductive system from destruction caused by an artificial insult; an amount effective to preserve, enhance, or revive ovarian function; an amount effective to prevent or ameliorate at least one menopausal syndrome; an amount effective to protect a female reproductive system from destruction caused by a chemical treatment, radiological treatment, surgical treatment, or combination; or an amount effective to protect a female reproductive system from pre-mature aging or destruction caused by a natural insult.

None of Perez, Spiegel, or Igarashi, either alone or in combination renders these claims obvious. In fact, none of the references, either alone or in any combination, provides an enabling disclosure of the present invention or teaches or suggests all of the limitations of the claims.

With regard to all claims and particularly regarding claims to protection of a female reproductive system from artificial insults (such as claims 1 and 46 and claims dependent therefrom), it is particularly significant that Perez's studies on the effects of sphingosine-1-phosphate (S1P) on the survival of oocytes exposed to doxorubicin are performed in *in vitro* cultures of oocytes. See, Perez, p. 1229, col. 1, lines 21-26. It is a commonly accepted principle that success *in vitro* does not provide a reasonable expectation of success *in vivo* or *ex vivo*. Such *in vitro* studies, at most, make it obvious to try to prevent damage to a female reproductive system from doxorubicin by administering S1P. Obviousness to try is not a proper standard for finding a claim obvious under 35 U.S.C. §103(a).

Further, Perez itself makes clear that the results of the *in vitro* study on oocytes presented in the reference do not establish a reasonable expectation of success *in vivo* or *ex vivo*, in ovaries, or in a reproductive system. For example, Perez points out that "fertility preservation would require maintenance of the entire follicle and not solely the oocyte." Perez, page 1230, col. 1, lines 6-7.

With regard to claims to protection of a female reproductive system from natural insults; preventing or ameliorating menopausal syndromes in women; and preserving, enhancing, or reviving ovarian function (such as claims 62, 33, and 27 and claims dependent therefrom), Perez makes no teaching or suggestion that treatment with S1P would be capable of achieving such goals. Nowhere does Perez even mention the use of S1P for such treatments.

Additionally, as Perez fails to enable and/or even suggest *in vivo* or *ex vivo* protection from artificial insults; protection of ovaries; protection of the reproductive system; protection from natural insults; preserving, enhancing, or reviving ovarian function; or preventing or ameliorating menopausal syndromes, Perez necessarily fails to teach or suggest the limitations, one of which is present in each independent claim, that an agent be administered in an amount effective to protect a female reproductive system from destruction caused by an artificial insult (Claim 1); to preserve, enhance, or revive ovarian function (Claim 27); to prevent or ameliorate at least one menopausal syndrome (Claim 33); to protect the reproductive system from destruction caused by a chemical treatment, radiological treatment, surgical treatment or combination (Claim 46); or to protect a female reproductive system from pre-mature aging or destruction caused by a natural insult (Claim 62).

As these limitations are also neither taught nor suggested in Spiegel or Igarashi, Perez in combination with either or both of Spiegel or Igarashi fails to teach all limitations of the claims, and a *prima facie* case of obviousness has not been established.

Spiegel does not teach or suggest protecting a female reproductive system from insults, be they natural or artificial; nor does it teach or suggest preventing damage from a

treatment, such as chemical treatment, radiological treatment, surgical treatment, and combinations thereof used to treat a disease, disorder, or condition. Likewise, Spiegel neither teaches nor suggests preserving, enhancing, or reviving ovarian function in mammals or preventing or ameliorating menopausal syndromes in women. In fact, Spiegel neither teaches nor suggests anything about the female reproductive system. Instead, Spiegel focuses on epidermal cells and neurodegenerative diseases. Thus, Spiegel neither teaches nor suggests the methods of the present invention and fails to teach or suggest the claim limitations lacking in Perez.

Additionally, Spiegel provides only *in vitro* results, and therefore suffers from the same deficiencies as Perez; even as to epidermal and neurodegenerative disorders, Perez dpes not provide any reasonable expectation of success of treatment *in vivo* or *ex vivo*.

Likewise, Igarashi does not teach or suggest protecting a female reproductive system from insults, be they natural or artificial; nor does it teach or suggest preventing damage from a treatment, such as chemical treatment, radiological treatment, surgical treatment, and combinations thereof used to treat a disease, disorder, or condition. Like Spiegel, Igarishi neither teaches nor suggests preserving, enhancing, or reviving ovarian function in mammals or preventing or ameliorating menopausal syndromes in women. Again like Spiegel, Igarishi neither teaches nor suggests anything about the female reproductive system.

Significantly, Igarashi fails to teach or suggest the claim limitations lacking in Perez. Although Igarashi may teach dosing information, as the Action suggests, the dosing information is irrelevant to the present invention.

Thus, neither Spiegel nor Igarashi provide the reasonable expectation of success lacking in Perez. Further, they do not teach or suggest the claim limitations lacking in Perez.

Furthermore, there is no motivation to combine the references. There is no motivation to combine Perez and Spiegel because Perez relates to damage to oocytes by cancer treatments and Spiegel relates to prevention of damage caused by aging and degenerative

diseases. Thus, Spiegel and Perez do not address treatment of the same condition. Igarashi addresses the prevention of metastasis, chemoinvasion, cell motility, and inflammation, which are all conditions that are very different from those addressed by either Perez or Spiegel.

For at least these reasons, Claims 1, 27, 37, 46, and 62 are unobvious over Perez, Spiegel, and Igarashi, taken alone or in any combination. Claims 2-23, 28-36, 47-61, and 63-71 are likewise unobvious over the references, at least because they depend either directly or indirectly from Claims 1, 27, 37, 46, or 62

CONCLUSION

Applicants submit that the subject application is in condition for allowance, and respectfully request that such action be taken. Attached hereto is a marked-up version of the changes made to the application by the current amendment. The attachment is captioned "Version with Markings to Show Changes Made." The Examiner is invited to contact Deborah Somerville, Esq. at (212)-908-6142 of Kenyon & Kenyon, New York, N.Y. to discuss any matter regarding this application.

Respectfully submitted,
KENYON & KENYON

Dated: 10 apr 2002

Jennifer King
Reg. No. 46,828

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Fax: (202) 220-4201

VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Amended) A method of protecting a female reproductive system against [a natural or] an artificial insult comprising: administering a composition comprising an agent that antagonizes one or more acid sphingomyelinase (*ASMase*) gene products, in an amount sufficient to protect said female reproductive system from [pre-mature aging or] destruction caused by said [natural or] artificial insult, wherein said administration is *in vivo* or *ex vivo*.

3. (Amended) The method of claim [1] 62 wherein said natural insult is a consequence of aging, genetic background, physiological factors, environmental factors, or a combination thereof.

27. (Amended) A method of preserving, enhancing, or reviving ovarian function in mammals comprising: administering [to said mammal an effective amount of] a composition comprising sphingosine-1-phosphate, or an analog thereof to said mammal in an amount effective to preserve, enhance, or revive ovarian function .

33. A method of preventing or ameliorating menopausal syndromes in women, comprising administering to women, at predetermined intervals, a composition comprising sphingosine-1-phosphate, or an analog thereof in an amount effective to prevent or ameliorate at least one menopausal syndrome.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/503,852	02/15/2000	Jonathan L. Tilly	2653/28	5439

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EXAMINER	
DI NOLA BARON, LILIANA	

ART UNIT	PAPER NUMBER
1615	11

DATE MAILED: 05/24/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/503,852	TILLY ET AL.	
	Examiner	Art Unit	
	Liliana Di Nola-Baron	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23,27-36 and 46-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23, 27-36 and 46-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

5/29/02

DETAILED ACTION

Receipt of Applicant's amendment, filed on April 10, 2002, is acknowledged.

Claim Objections

1. Claim 3 is objected to for being improperly dependent on subsequent claim 62. A series of singular dependent claims is permissible in which a dependent claim refers to a preceding claim which, in turn, refers to another preceding claim. It should be kept in mind that a dependent claim may refer to any preceding independent claim, but not to a subsequent independent claim. Appropriate correction is required.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-23, 27-36 and 46-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Perez et al. in view of Spiegel and further in view of Igarashi et al.

The claimed invention refers to methods of protecting female reproductive system, preserving or reviving ovarian function, or ameliorating menopausal syndromes in women, comprising administering a composition comprising sphingosine-1-phosphate (SPP).

Perez et al. indicates that conventional cancer therapies kill normal cells and one of the most sensitive noncancerous cell type is the ovarian germ cell, and teaches that apoptosis induced by doxorubicin is blocked by sphingosine-1-phosphate (See e.g., p. 1228 and Abstract). Perez et al. teaches that exposure of women to a wide spectrum of agents that damage the ovary generally leads to irreversible sterility (See e.g., p. 1228) and the data from the study provide a strong impetus to manipulate death effector pathways in oocytes, in vivo, as a potential means to overcome infertility associated with cancer treatment (See e.g., p. 1231).
Perez et al. does not specify the method and dosage of administration of compositions comprising SPP.

Spiegel provides methods of retarding apoptosis in degenerative diseases, including neurodegenerative diseases and aging, by administration of sphingosine-1-phosphate and derivatives thereof (See e.g., col. 1, lines 9-17). Spiegel teaches that compositions containing SPP may be administered directly to the cells or parenterally to obtain concentrations of 0.1-100 μM, as well as to the epithelial tissues, such as the rectum and the vagina (See e.g., col. 1, line 46 to col. 2, line 42).

4. Igarashi et al. discloses a method of inhibiting tumor cell chemoinvasion, comprising contacting the tumor cells with an inhibitory amount of sphingosine-1-phosphate (See e.g., col. 1, line 57 to col. 2, line 48). Igarashi et al. provides methods of inhibiting tumor cell chemoinvasion, comprising administering to a host in need of treatment an inhibitory amount of sphingosine-1-phosphate and teaches that said inhibitory amount can be determined using art-

recognized methods, such as dose response curves, or clinical trials, and sphingosine-1-phosphate can be administered orally, parenterally and topically, with suitable doses of sphingosine-1-phosphate depending upon the particular medical application and that the number of doses, daily dosage and course of treatment may vary from individual to individual (See e.g., col. 7, lines32-65).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to apply the teachings of Perez et al. and Spiegel to device methods of protecting the female reproductive system, reviving the ovarian function or ameliorating menopausal syndromes in women, comprising administering SPP compositions, and determining the mode and dosage of administration according to the teachings of Igarashi et al. Because of the teachings of Spiegel, that sphingosine-1-phosphate is effective in treating aging diseases, and the teachings of Igarashi et al., that sphingosine-1-phosphate inhibits tumor cell chemoinvasion, one of ordinary skill in the art would have a reasonable expectation that the methods claimed in the instant application would be successful. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

5. Applicant's arguments filed on April 10, 2002 have been fully considered but they are not persuasive.

6. Applicant argues that none of the references alone or in combination teaches Applicant's claimed invention. Specifically, Applicant argues that Perez et al. discloses studies, which were

performed in vitro and does not teach protection of a female reproductive system and administration of an effective amount of the active agent. and Spiegel and Igarashi et al. do not teach anything about the female reproductive system. Additionally, Applicant argues that there is no motivation to combine the references. In response to said arguments, it is noted that Perez et al. teaches that exposure of women to a wide spectrum of agents that damage the ovary generally leads to irreversible sterility (See e.g., p. 1228) and the data from the study provide a strong impetus to manipulate death effector pathways in oocytes, in vivo, as a potential means to overcome infertility associated with cancer treatment (See e.g., p. 1231). Spiegel teaches the use of sphingosine-1-phosphate (SPP) to retard apoptosis in degenerative diseases, including aging, which is defined by Applicant as a natural insult (See Applicant's specification, p. 15). Additionally, Spiegel teaches that SPP may be administered to the epithelial tissues, such as the rectum and the vagina (See e.g., Col. 1, line 46 to col. 2, line 26). Igarashi et al. provides methods of inhibiting tumor cell chemoinvasion, comprising administering to a host in need of treatment an inhibitory amount of sphingosine-1-phosphate and teaches that said inhibitory amount can be determined using art-recognized methods, such as dose response curves, or clinical trials, and sphingosine-1-phosphate can be administered orally, parenterally and topically (See e.g., col. 7, lines32-65). Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to combine the teachings of Perez et al. and Spiegel to device methods of protecting the female reproductive system, reviving the ovarian function or ameliorating menopausal syndromes in women, comprising administering SPP compositions, and determining the mode and dosage of administration according to the teachings of Igarashi et

al. The expected result would have been a successful method of protecting a female reproductive system against natural or artificial insults.

7. In response to applicant's argument that there is no suggestion to combine the references. the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Perez et al. contemplates methods of treatment of the female reproductive system using sphingosine-1-phosphate in vivo based on studies, which were performed in vitro. Spiegel teaches the use of sphingosine-1-phosphate (SPP) to retard apoptosis in degenerative diseases, including aging, and Igarashi et al. provides methods of inhibiting tumor cell chemoinvasion, comprising administering to a host in need of treatment an inhibitory amount of sphingosine-1-phosphate. Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to combine the teachings of Perez et al. and Spiegel to device methods of protecting the female reproductive system, reviving the ovarian function or ameliorating menopausal syndromes in women, comprising administering SPP compositions, and determining the mode and dosage of administration according to the teachings of Igarashi et al. The expected result would have been a successful method of protecting a female reproductive system against natural or artificial insults.

Conclusion

8. Claims 1-23, 27-36 and 46-71 are rejected.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Liliana Di Nola-Baron whose telephone number is 703-308-8318. The examiner can normally be reached on Monday through Thursday, 5:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on 703-308-2927. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3592 for regular communications and 703-305-3592 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 308-1234/ 1235.

May 23, 2002

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600